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RESEARCH ARTICLE

MRI-based risk stratification for recurrent ischemic stroke in embolic stroke of undetermined source

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Abstract

Objective: Leukoaraiosis and other brain MRI-assessed parameters were shown to be associated with recurrent stroke in this population. We aimed to develop an MRI-based predictive tool for risk stratification of ESUS patients. **Methods**: We retrospectively assessed consecutive patients who were diagnosed with ESUS and underwent brain MRI and performed a multivariable analysis with the outcome of recurrent stroke/TIA. Based on the coefficient of each covariate, we generated an integer-based point scoring system. The discrimination and calibration of the score were assessed using the area under the receiver operator characteristic curve, net reclassification improvement, integrated discrimination improvement, calibration curve, and decision curve analysis. Also, we compared the new score with a previously published score (ALM score). **Results**: Among 176 patients followed for an overall period of 902.3 patient-years (median of 74 months), there were 39 recurrent ischemic stroke/TIAs (4.32 per 100 patient-years). Fazekas score (HR: 1.26, 95% CI: 1.03–1.54), enlarged perivascular space (EPVS) (HR: 2.76, 95% CI: 1.12–6.17), NIHSS at admission (HR: 1.11, 95% CI: 1.02–1.18), and infarct subtypes (HR: 2.88, 95% CI: 1.34–6.17) were associated with recurrent stroke/TIA. Accordingly, a score (FENS score) was developed with AUC-ROC values of 0.863, 0.788, and 0.858 for 1, 3, and 5 years, respectively. These were significantly better than the AUC-ROC of ALM score (0.635, 0.695, and 0.705, respectively). The FENS score exhibited better calibration and discrimination ability than the ALM score (Hosmer–Lemeshow test χ^2: 4.402, $p = 0.819$). **Conclusion**: The MRI-based FENS score can provide excellent predictive performance for recurrent stroke/TIA and may assist in risk stratification of ESUS patients.

Introduction

Embolic strokes of undetermined source (ESUS) account for 17% of all ischemic strokes with a considerable rate of stroke recurrence of approximately 4.5%–5% per year.[1–4] The optimal antithrombotic strategy in patients with ESUS is not clear.[5] It was suggested that oral anticoagulants may be preferable to aspirin, but three randomized controlled trials did not confirm this hypothesis.[2,6,7] Currently, a randomized trial aims to assess whether oral anticoagulation with apixaban is superior to aspirin in patients with ESUS and evidence of atrial cardiopathy.[8] In addition, patients with ESUS need further diagnostic work-up which is individualized and complex, including (but not limited to) several diagnostic modalities like cardiac and arterial multimodal imaging and monitoring of the heart rhythm.[9]

In this context, given the need for further research to optimize preventive strategies in ESUS patients, and the need to individualize the diagnostic work-up in these patients, a reliable prediction tool to stratify the risk of stroke recurrence in ESUS could be useful. A previously published prognostic score based on age, leukoaraiosis, and multiterritorial infarcts on brain CT or MRI (ALM score) showed that it can assist in the identification of patients with ESUS at high risk for stroke recurrence.[10] We hypothesized that assessing (a) leukoaraiosis in a quantitative manner (i.e., using the Fazekas score) rather than qualitatively (i.e., presence or not) and (b) assessing also other

MRI-based parameters, would be associated with higher predictive performance. We tested this hypothesis in the present study, in which we analyzed a previously described cohort of ESUS patients with high-resolution brain MRI (HR-MRI), aiming to develop a predictive tool for the identification of ESUS patients at high risk for recurrent stroke or transient ischemic attack (TIA).

Methods

Patients

This study was approved by the Institutional Review Board of the General Hospital of Northern Theater Command, and informed consent was waived. The analysis was performed in the same ESUS cohort, which has been reported in detail previously.[11] Briefly, consecutive patients with unilateral anterior circulation stroke who fulfilled the ESUS criteria and had an HR-MRI within 1 week of onset were enrolled between 01/2015 and 12/2019 in the stroke center of the General Hospital of Northern Theater Command in Shenyang, China. ESUS was defined according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group as a nonlacunar brain infarct in the absence of the following: (1) extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; (2) major risk cardioembolic source; and (3) any other specific cause of stroke (e.g., arteritis, dissection, migraine/vasospasm, and drug misuse).[12] Patients with nonstenosing carotid plaque ≥3 mm detected by computed tomography angiography (CTA) or carotid ultrasonography; or aortic arch atherosclerotic plaque with ulceration or ≥4 mm by CTA or transesophageal echocardiogram; or endovascular treatment such as balloon dilatation and stent; or bilateral infarcts; or previous radiation therapy to head or neck and malignant tumor were excluded.

Data collection

The baseline variables collected included demographic data, clinical characteristics, a range of laboratory indicators, and neuroimaging data (including T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging (DWI), and fluid-attenuated inversion recovery). Follow-up assessment was performed in person or by telephone from 06/2022 to 07/2022 to register all concomitant medications, severe adverse events, stroke or TIA recurrence, other vascular events, and death. The recurrence of stroke or TIA was assessed by physicians based on clinical symptoms and neuroimaging. In the case of multiple recurrent strokes or TIAs in a specific patient, the first recurrence was used in this analysis.

Brain imaging

All MRI scans were performed on 3.0-T MRI scanners (GE Discovery MR750, GE Medical Systems, Milwaukee, Wisconsin) using an 8-channel head coil with standardized acquisition protocols. We assessed imaging markers of cerebral small vessel disease (CSVD) burden, Fazekas score, and infarct subtypes. The burden of CSVD includes lacunes and white matter hyperintensities (WMH) of presumably vascular origin, enlarged perivascular spaces (EPVS), and cerebral microbleeds (CMB).[13] We assessed the number of lacunes, EPVS (EPVSs in the centrum of the oval and the basal ganglia, respectively), and CMBs (lobar and deep/infratentorial CMBs, respectively) in both hemispheres of the brain. The basal ganglia EPVS was scored on a 5-grade semiquantitative scale ranging from 0 to 4 (0: no EPVS; 1: 1 ~ 10 EPVS; 2: 11 ~ 20 EPVS; 3: 21 ~ 30 EPVS; and 4: ~40 EPVS). We also determined the total CSVD burden using these four markers based on an ordinal "CSVD score" (range: 0 to 4). One point was awarded for any of the following definitions: ≥1 lacunes; ≥1 cerebral microbleed; moderate to severe (grade 2–4) EPVS in basal ganglia; and periventricular WMH Fazekas 3 (extending into deep white matter) and/or deep WMH 2–3 (early confluent).

The Fazekas scale was used to score the periventricular and deep white matter lesions (PVWM and DWM, respectively) separately (range: 0 to 3), and the scores of the two parts were summed to calculate the total score (range: 0–6 points).[14] The scoring criteria for PVWM were as follows: 0: absent; 1: "caps" or pencil-thin lining; 2: smooth "halo"; and 3: irregular extending into DWM. The scoring criteria for PVWM were as follows: 0: absent; 1: punctate; 2: beginning confluence; and 3: large confluent areas.

In line with our recent study,[15] ESUS was categorized into two types according to the DWI-assessed infarct topography and the anatomical characteristics of intracranial arteries supplying the infarct territory: (1) deep ESUS, defined as a single nonlacunar infarct located only in the basal ganglia and/or periventricular white matter supplied by the lenticulostriate arteries; and (2) cortical with/without deep ESUS, defined as multiple cortical infarcts (at least two infarct lesions) or the coexistence of deep and cortical infarcts.

Brain magnetic resonance images were reviewed independently by two experienced neurologists (X.Q.L. and Y.J.D.) who were blinded to the clinical data. In case of disagreement, a third adjudicator (D.W.) was invited for a final decision which was resolved by majority opinion. Images with poor quality were excluded from the final analysis. Qualitative and quantitative analyses were performed using ImageJ version 1.49 (National Institutes of Health).

Statistical analysis

Continuous variables were expressed as medians [interquartile range (IQR)], and nominal variables are given as count and absolute percentages. The normality of distribution for continuous variables was evaluated using the Kolmogorov–Smirnov goodness-of-fit test. Differences between proportions were assessed by Fisher exact test or the χ^2 test, when appropriate.

Multivariate cox regression analysis was performed to identify predictors independently associated with recurrent stroke or TIA using a backward stepwise method that included all variables with a probability value <0.10 in the univariate analysis. The following covariates were included in the analysis: age, NIHSS at admission, infarct subtypes (deep ESUS and nondeep ESUS), Fazekas score, CSVD burden, EPVS, and WMH. A fitted set of all independent predictors was considered as the final multivariable model. Regression coefficients and hazard ratios (HRs) with 2-sided 95% confidence intervals (CI) for each of the variables included in the model, were calculated. To test for collinearity between the covariates of the final multivariable model, we calculated the tolerance and variance inflation factor (VIF) of each covariate.

Based on the coefficient of each independent covariate in the fitted multivariable model, we constructed an integer-based point scoring system by dividing each covariate with the smallest coefficient and then rounded to the nearest integer; the overall score was calculated as the sum of the covariates' weighted scores. Individual risk scores of all predictors were summed and a total risk score was assigned to each patient. To ensure the reliability of the model, we performed the analysis as follows. First, the patients from the cohort were divided into low- and high-risk groups based on the median of the total score. Patient risk heat plot, risk curve, and survival status plot were performed, respectively, to show the risk score and vital status of individuals. Second, based on the bootstrap method, repeated sampling 1000 times was used to internally verify the model, and the consistency index (C-index) value was calculated. Next, we externally validated the ALM score in our cohort of ESUS patients and compared it with the new score. We used the Kaplan–Meier product limit method to estimate the cumulative probability of stroke recurrence in two risk groups between two score tools. Differences in Kaplan–Meier curves were evaluated with the log-rank test. Discriminative performance was measured by calculation of the area under the receiver operating characteristic curve (AUC-ROC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) for 1-, 3-, and 5-year recurrence. The DeLong test was used to compare the difference between the AUC of different models.[16] NRI and IDI are two mutually complementary validation methods to compare the accuracy and predictive ability of two prediction models.[17] The difference between NRI and IDI is that the NRI only considers the improvement setting a certain cutoff point while the IDI inspects the overall improvement of the model. If the values of NRI and IDI are over 0, the prediction performance of the new model is improved than existing models in sensitivity and specificity.[18] Finally, calibration was tested using the Hosmer–Lemeshow (HL) test and calibration plot with bootstraps of 1000 resamples, which were drawn to compare predicted probabilities with observed probabilities. Decision curve analysis (DCA) was performed in two scores to evaluate the clinical usefulness of the new score by calculating the net benefit for a range of threshold probabilities.[19,20] Statistical analysis was performed using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-tailed. We deemed statistical significance at $p = 0.05$.

Results

Baseline characteristics of the cohort

Among 243 eligible patients with complete MRI data, 67 patients lost to follow-up were excluded from the analysis (Fig. 1). The final cohort included 176 patients (43.3% men, median age 65 years, interquartile range [IQR] 55.25–75) who were followed for an overall period of 902.3 patient-years. During a median follow-up of 74 months, 39 patients (22.1%) had a recurrent stroke or TIA, corresponding to 4.32 (95% CI 3.13–5.91) recurrences per 100 patient-years. The baseline characteristics of the patients with vs. without recurrent stroke or TIA are summarized in Table 1.

Univariable and multivariable analyses

The univariable analysis revealed that age, NIHSS at admission, infarct subtypes, Fazekas score, DWM, PVWM, SVD burden, EPVS, and WMH were related to recurrent ischemic events. In multivariable cox regression analysis, NIHSS at admission (HR: 1.11, 95% CI: 1.03–1.18, $p = 0.004$), infarct subtypes (HR: 2.88, 95% CI: 1.34–617, $p = 0.006$), Fazekas score (HR: 1.26, 95% CI: 1.03–1.54, $p = 0.023$), and EPVS (HR: 2.76 95% CI: 1.12–6.17, $p = 0.026$) were identified as independent predictors of recurrence events (Table 2).

Predictive model development

The Fazekas score, EPVS, NIHSS score at admission, and the subtype of the infarct were used to build a

Table 1. Baseline characteristics of ESUS patients with and without recurrent stroke.

	Total (n = 176)	Recurrent (n = 39)	Nonrecurrent (n = 137)	p value
Demographic characteristics				
Age, y, median (IQR)	69 (55.25 ~ 75)	63 (56 ~ 70)	60 (52 ~ 68)	0.041
Male (%)	119 (67.6)	23 (60.5)	96 (69.6)	0.3
Medical history				
Hypertension (%)	91 (51.7)	24 (63.2)	67 (48.6)	0.111
Diabetes mellitus (%)	44 (25)	12 (31.6)	32 (23.2)	0.225
Stroke or transient ischemic attack (%)	34 (19.3)	9 (23.7)	25 (18.1)	0.358
Coronary artery disease (%)	23 (13.1)	7 (18.4)	16 (11.6)	0.273
Smoking (%)	79 (44.9)	15 (39.5)	64 (46.4)	0.425
Drinking (%)	73 (41.5)	16 (42.1)	57 (41.3)	0.972
NIHSS at admission (IQR)	3 (1 ~ 7.75)	5 (3 ~ 9)	3 (1 ~ 6)	0.008
CSVD, median (IQR)	2 (1 ~ 3)	2 (1 ~ 3)	2 (1 ~ 3)	0.009
White matter hyperintensity (%)	68 (38.6)	21 (55.3)	47 (34.1)	0.014
Enlarge perivascular space (%)	72 (40.9)	22 (57.9)	50 (36.2)	0.011
Cerebral microbleed (%)	99 (56.3)	21 (55.3)	78 (56.5)	0.941
Lacunar (%)	98 (55.7)	24 (63.2)	74 (53.6)	0.293
Fazekas score, median (IQR)	3 (2 ~ 4)	3 (3 ~ 4)	2 (1 ~ 3)	<0.001
Periventricular white matter (IQR)	2 (1 ~ 2)	2 (1 ~ 2.25)	1 (1 ~ 2)	<0.001
Deep white matter (IQR)	1 (0 ~ 2)	1 (1 ~ 2)	1 (0 ~ 1)	0.001
Infarct subtypes				
Deep ESUS (%)	84 (48)	10 (26.3)	74 (54.0)	0.001
Nondeep ESUS (%)	92 (52)	29 (76.3)	63 (45.2)	
Ipsilateral intracranial complicated plaque (%)	87 (49.4)	20 (52.6)	67 (48.6)	0.408
Atrial cardiopathy (%)	70 (39.8)	16 (42.1)	54 (39.1)	0.68
Antithrombotic therapy				0.726
Antiplatelet therapy (%)	152 (86.4)	35 (89.7)	117 (85.4)	
Anticoagulant therapy (%)	6 (3.4)	1 (2.6)	5 (3.6)	
Anticoagulation and antiplatelet (%)	4 (2.3)	0	4 (2.9)	
Laboratory tests				
Cholesterol (mg/dL)	176.3 (145.7 ~ 205.9)	190 (149 ~ 224.1)	171.8 (145.3 ~ 202.9)	0.244
High-density lipoprotein (mg/dL)	38.3 (32.5 ~ 42.8)	39.2 (34.4 ~ 44.2)	38.3 (32.5 ~ 42.5)	0.272
Low-density lipoprotein (mg/dL)	103 (80.4 ~ 128.3)	110.8 (87.1 ~ 141.8)	100.3 (79.1 ~ 126.9)	0.134
Cystatin C (mg/L)	0.9 (0.7 ~ 1)	0.9 (0.7 ~ 1.1)	0.9 (0.7 ~ 1)	0.394
Glycosylated hemoglobin	5.8 (5.5 ~ 6.2)	6 (5.7 ~ 6.6)	5.8 (5.5 ~ 6.1)	0.249
Homocysteine (μmol/L)	11.6 (9.2 ~ 15.3)	11.9 (9.6 ~ 15.6)	11.5 (9 ~ 14.9)	0.923
Uric acid (μmol/L)	305 (266.3 ~ 375)	314.5(269 ~ 373.5)	305 (263.8 ~ 376.5)	0.933
Glucose (mmol/L)	5.98 (5.13 ~ 7.96)	6.33 (5.23 ~ 9.62)	5.92 (5.01 ~ 7.71)	0.286
Hemoglobin (g/L)	138.96 ± 16.93	136.95 ± 15.15	139.53 ± 17.42	0.402

Values are mean SD or n (%). Numerical variables were analyzed with Student's t-test. For categorical variables, chi-squared or Fisher exact test was used.

CSVD, cerebral small vessel disease burden; ESUS, embolic stroke of undetermined source; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

model for the prediction of recurrent stroke/TIA (FENS score, by the initial letter of each covariate). Based on the β-coefficients of these covariates, a pointing system was assigned to each covariate (Table 3). The tolerance of the covariates in the final multivariate model ranged between 0.88 and 0.955, and the mean VIF was 1.078 (range 1.047–1.137). In addition, a risk score model was constructed using the aforementioned formula, which contained risk score ranking, survival status, and heat map (Fig. 2). The results showed that the recurrent risk increased with the FENS score increase (Fig. 2A,B). According to the median of the FENS score distribution, we defined two stroke risk groups: the lower risk group: a score: 0–7, and the higher risk group: a score: 8–15. The heatmap (Fig. 2C) revealed the dynamic contribution of the four risk factors to predicting recurrent stroke/TIA events in low- vs high-risk population. Compared with the low-risk group, the risk of recurrent stroke/TIA was significantly higher in patients with high risk (HR: 3.06, 95% CI: 1.45–6.46, Fig. 3A). The C-index value for internal validation of the model was 0.786.

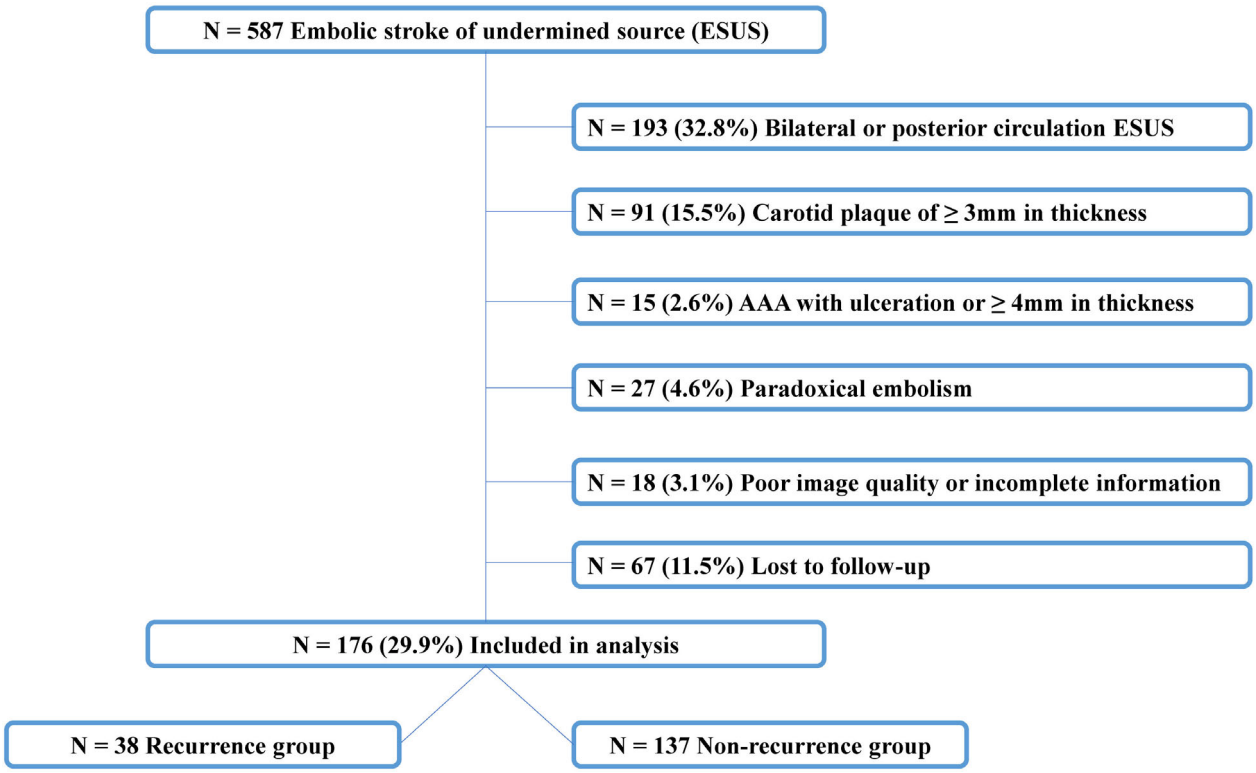

Figure 1. Flow diagram of study enrollment. AAA, aortic arch atherosclerosis; ESUS, embolic stroke of undetermined source; NSIP, nonstenotic intracranial plaque.

Table 2. Univariable and multivariable analyses of stroke recurrence.

	Univariable analysis			Multivariate analysis		
Variable	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.03	1.00–1.06	0.041	1.00	0.97–1.03	0.819
NIHSS at admission	1.09	1.02–1.17	0.007	1.11	1.03–1.18	0.004
Infarction subtypes	3.326	1.61–6.85	0.001	2.88	1.34–6.17	0.006
Fazekas score	1.54	1.27–1.88	<0.001	1.26	1.03–1.54	0.023
CSVD burden	1.44	1.10–1.91	0.009	1.15	0.85–1.56	0.381
EPVS	2.28	1.22–4.42	0.011	2.76	1.12–6.17	0.026
WMH	2.21	1.18–4.25	0.014	1.26	0.59–3.02	0.065

CI, confidence interval; HR, hazard ratio.

Table 3. Scores corresponding to each category of risk factors.

Risk factor	β-coefficients	Adjusted HR (95%CI)	*p* value	Score points
NIHSS at admission	0.09	1.094 (1.022–1.17)	0.009	
<4				0
≥4[a]				0–9
Fazekas score	0.214	1.239 (1.023–1.59)	0.04	
0–2				0
3–4				1
5–6				2
Infarct subtypes	1.077	2.936 (1.365–6.292)	0.006	
Deep ESUS				0
Nondeep ESUS				3
EPVS	0.784	2.191 (1.088–4.407)	0.028	
No				0
Yes				3

NIHSS, National Institutes of Health Stroke Scale.
[a]1 score per 4-point increase.

Comparisons between the FENS score and ALM score

We externally validated the previously reported ALM score in our ESUS cohort and compared the discriminative performance of the FENS score with the ALM score. In Kaplan–Meier analysis, the FENS score (Fig. 3A) and the ALM score (Fig. 3B) were able to identify recurrence risk, but the FENS score had better discriminatory ability than the ALM score ($p < 0.001$ vs $p = 0.044$). The AUC

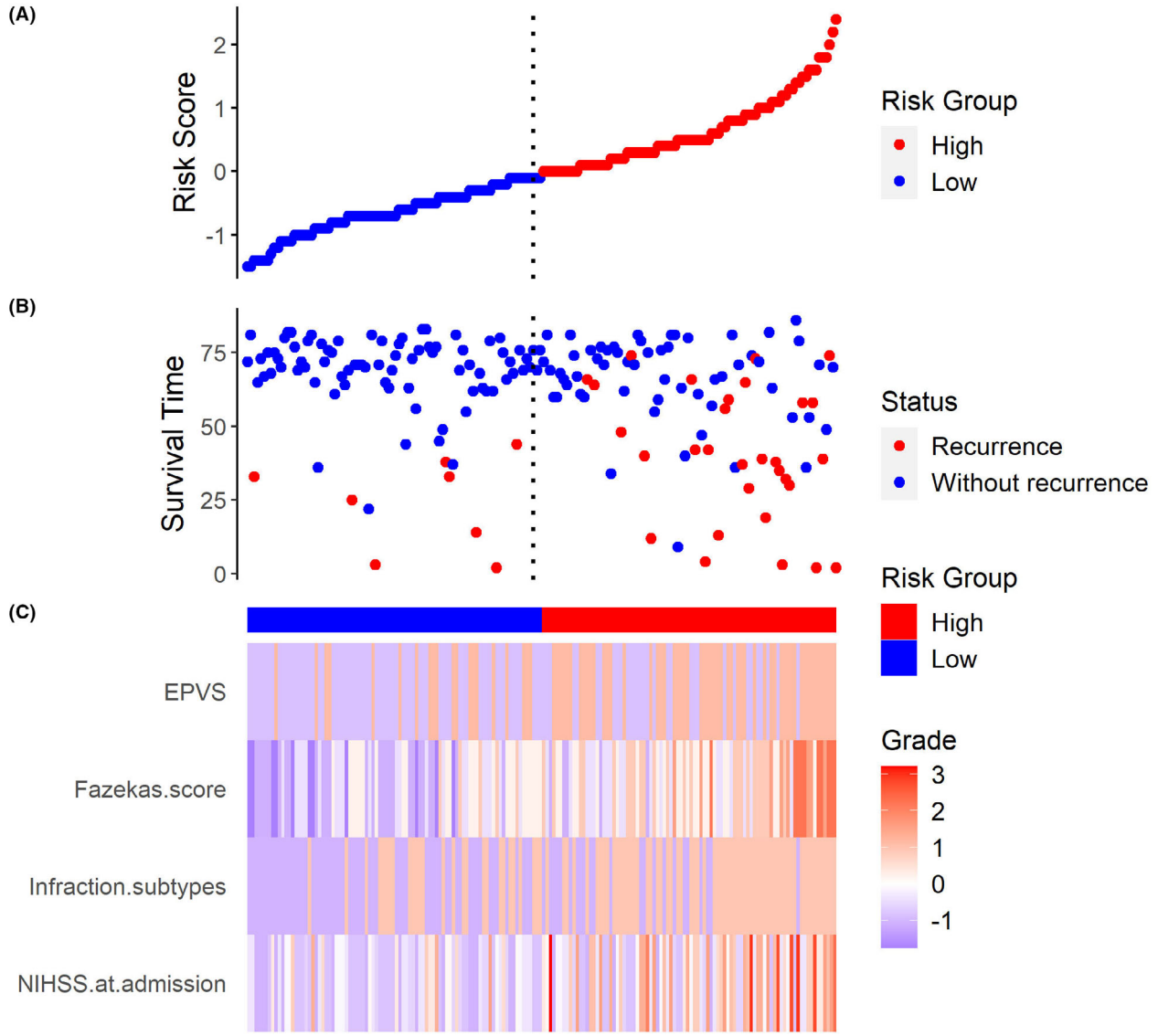

Figure 2. Risk plot of model. (A) Risk score distribution for patients; (B) ESUS patient survival time; (C) expression heat map for the four risk factors incorporated into the prediction model.

values at 1, 3, and 5 years of FENS score were 0.863, 0.788, and 0.858 (Fig. 4A), which was significantly better than the AUC values of ALM score (0.635, 0.695, and 0.705, respectively) (Fig. 4B). The values of AUC-ROC in the FENS score were greater than that in the ALM score (Delong test, $p < 0.05$, Table 4). Furthermore, NRI and IDI showed that the FENS score exhibited higher discriminative performance to predict recurrent stroke/TIA than the ALM score (Table 4). Calibration plots of the FENS score (Fig. 5A–C) and ALM score (Fig. 5D–F) showed that their predictive and actual survival curves were close, indicating similar predictive accuracy. Hosmer–Lemeshow test showed that both the FENS score (χ^2: 4.402, $p = 0.819$) and the ALM score (χ^2: 7.411, $p = 0.493$) were well fitted. The DCA showed that the FENS score processed greater net benefit for predicting the recurrence of ischemic events than the ALM score (Fig. 6).

Discussion

The present analysis proposes a new approach for risk stratification of ESUS patients based on stroke severity assessed by the NIIHSS score and three MRI-based covariates, that is, the degree of leukoaraiosis, the infarct subtype, and EPVS. The proposed FENS score shows excellent predictive performance and accuracy to identify

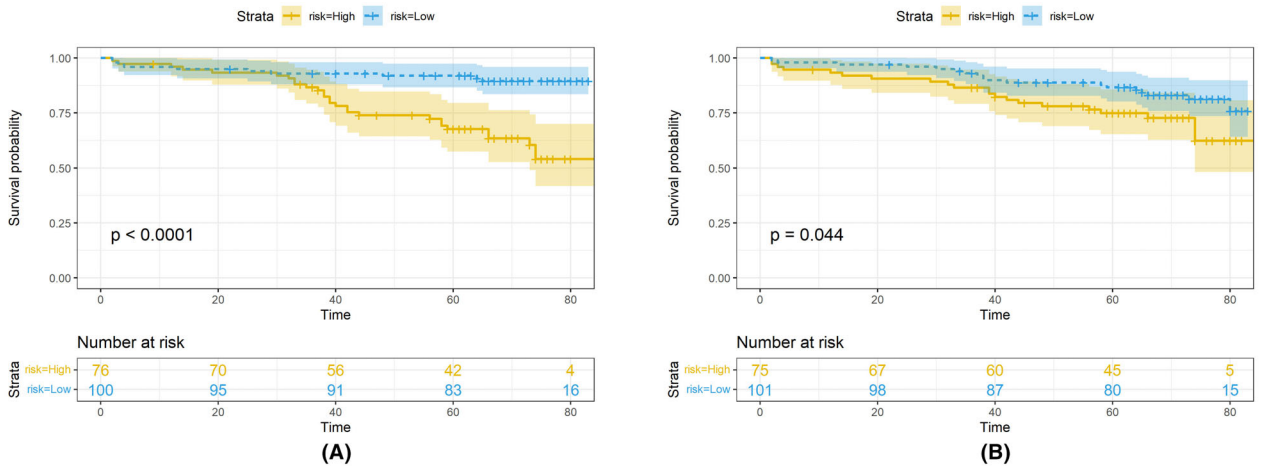

Figure 3. Kaplan–Meier curves of cumulative probabilities of recurrent ischemic events across risk categories in the cohort. Recurrence rates of ischemic events as the primary endpoint were significantly higher in patients with high risk than in patients with low risk. (A) FENS score. (B) LAM score.

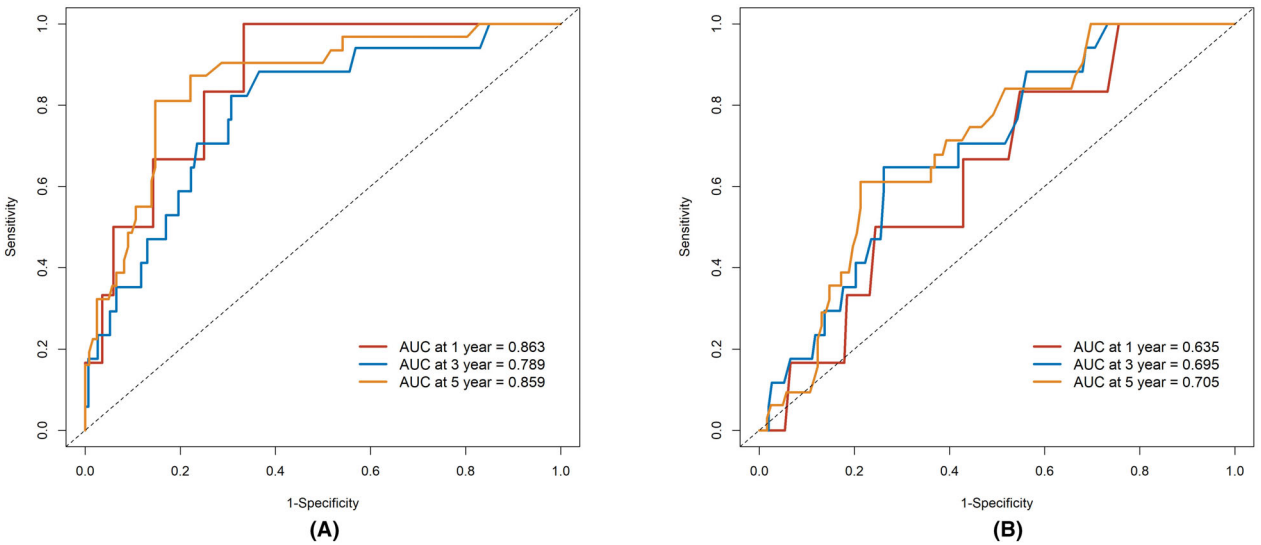

Figure 4. Receiver operating characteristic (ROC) curves. ROC curves for 1-, 3-, and 5-year survival rates from the risk score model. ROC, receiver operating characteristic; AUC, area under the curve. (A) FENS score. (B) LAM score.

ESUS patients at high risk for recurrent stroke/TIA. Patients with a FENS score of ≥8 have three times higher risk of recurrence stroke/TIA compared with patients with a score of <8.

The proposed score could be useful in the research setting and, in particular, in the design of future trials of stroke prevention in ESUS patients. In specific, it could guide trial eligibility criteria for patient selection, aiming to identify those patients who have high risk for a recurrent stroke/TIA. In this way, higher event rates could be expected in a trial that focuses predominantly on high-risk patients, which could have implications for the size of the study population and the necessary follow-up duration, and therefore, for the logistics of the trial. The proposed score could be useful also in the clinical setting, as it could inform decisions about the diagnostic work-up; for example, high-risk patients could be better candidates for more thorough, complicated, or resource-demanding investigations.

Our finding that NIHSS, infarct subtypes, leukoaraiosis, and EPVS are independently associated with recurrent ischemic stroke/TIA in ESUS patients is consistent with previous studies. It was previously shown that when NIHSS score increased by 1 point, the risk of stroke

Table 4. Comparison of the prediction ability between two models.

	Variable	FENS score (95%CI)	ALM score (95%CI)	(95%CI)	*p* value
	AUC	0.863 (0.761–0.965)	0.635(0.443–0.827)		0.018
1-year	NRI			0.186 (0.12–0.219)	0.025
	IDI			0.086 (0.01–0.15)	0.043
	AUC	0.788 (0.679–0.898)	0.695 (0.579–0.810)		0.015
3-year	NRI			0.269 (0.081–0.524)	0.037
	IDI			0.074 (0.01–0.143)	0.03
	AUC	0.858 (0.789–0.930)	0.704 (0.612–0.797)		<0.001
5-year	NRI			0.337 (0.043–0.554)	0.003
	IDI			0.112 (0.013–0.243)	0.016

AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement; ROC, receiver operating characteristic.

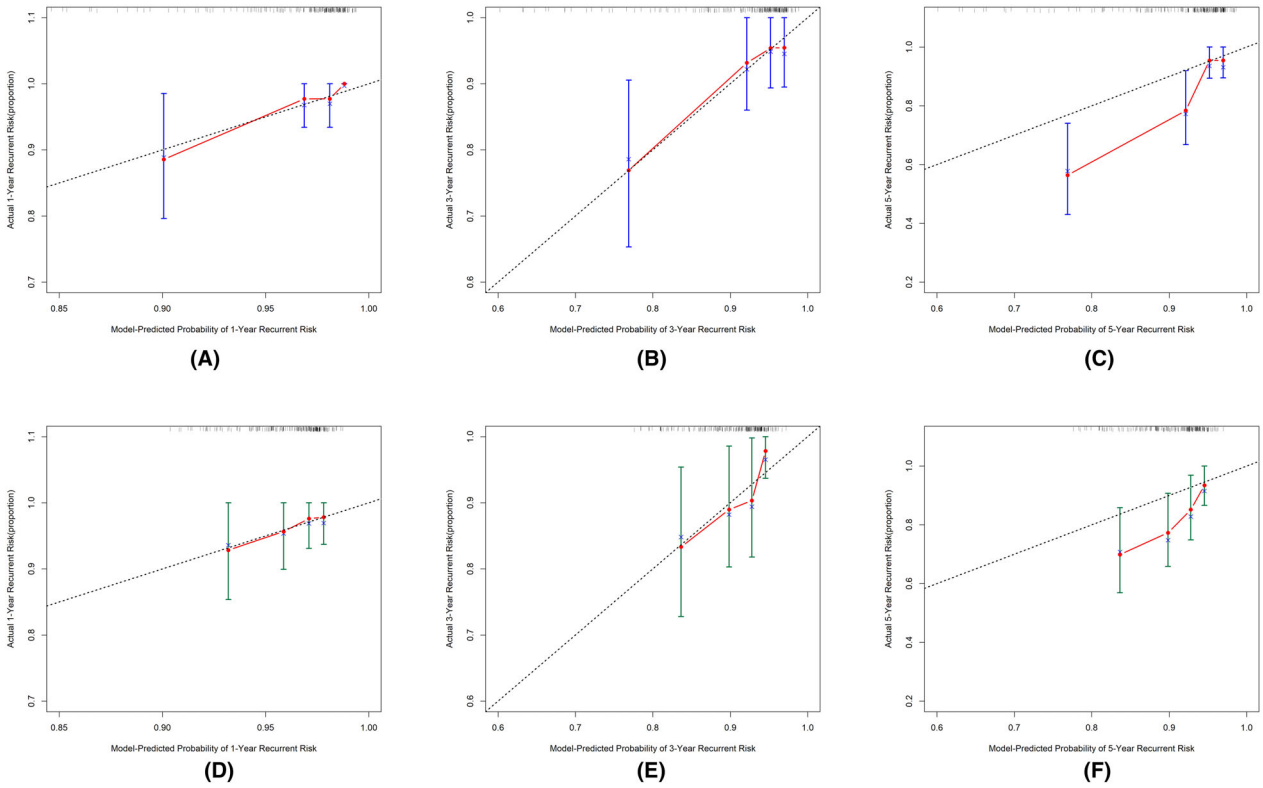

Figure 5. Calibration plot of the FENS score and ALM score. Calibration plots of the FENS score (A–C) and ALM score (D-F) for predicting recurrence ischemic events in ESUS patients.

recurrence was increased by 2% to 5%.[21] Also, CSVD burden, leukoaraiosis, and EPVS have been extensively found to be associated with stroke recurrence.[22–26] It is worth noting that the glymphatic system, as a new fluid-clearance pathway in brain,[27,28] has been recently found to be associated with WMHs, lacunae, cerebral microbleeds, and EPVS in patients with CSVD.[29,30] Therefore, potential connection between glymphatic clearance dysfunction and CSVD may be involved in the recurrence of ESUS. In addition, we recently assessed the different etiologies underlying deep and nondeep ESUS subtypes,[15] but the relationship of this kind of infarct subtypes to the recurrence of cerebral ischemic events in ESUS patients was never investigated. This is the first report of the close association of nondeep ESUS with recurrent stroke or TIA. This finding seems plausible as arterial or cardiogenic embolism should be common causes of nondeep ESUS, while nondeep ESUS may share a similar cause

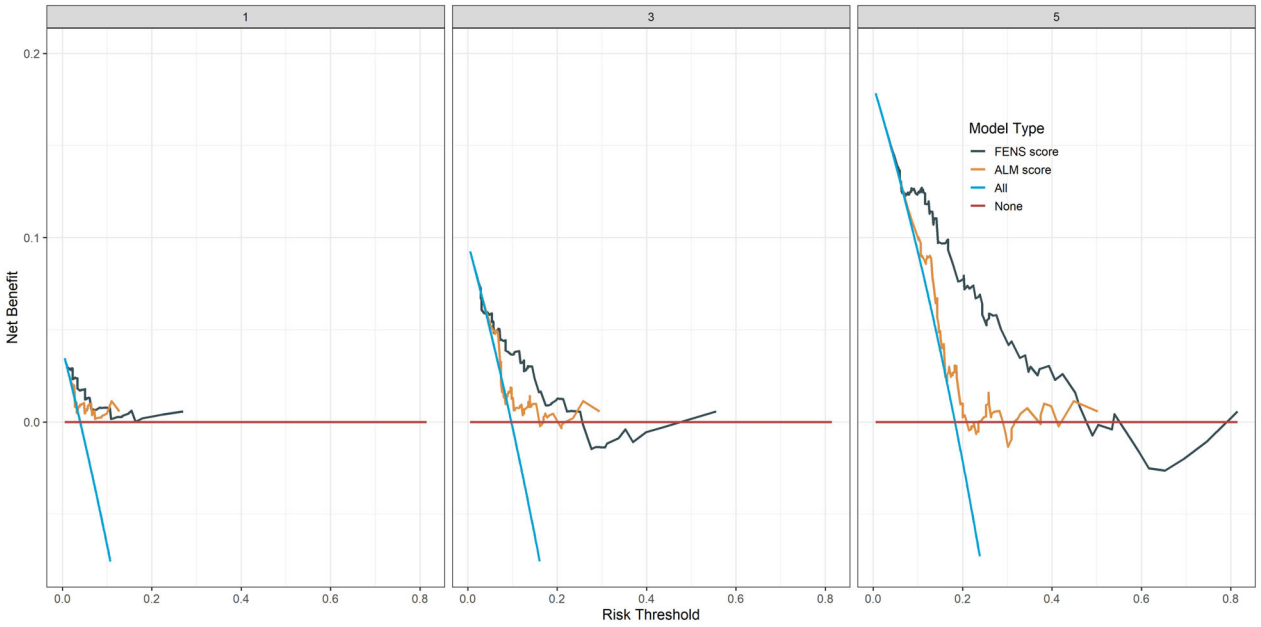

Figure 6. Decision curve analysis for the FENS score and the ALM score. Decision curve analysis for the FENS score and the ALM score. A horizontal line indicates that all samples are negative and not treated, with a net benefit of zero. An oblique line indicates that all samples are positive. The net benefit is a backslash with a negative slope.

with multiterritorial infarct, which was associated with recurrent stroke.[10,31,32] In turn, the significant difference in recurrent risk between deep and nondeep ESUS subtypes further supported their distinct etiologies.

One of the covariates included in the previously proposed ALM score is leukoaraiosis which was assessed in a qualitative way, that is, its presence on brain CT or MRI. Although this is convenient for health care settings with limited resources for brain MRI, it is suboptimal for settings where MRI is easily available given the clear superiority of MRI over CT for the assessment of the degree of leukoaraiosis. The FENS score which is proposed here assesses leukoaraiosis in a quantitative way according to the Fazekas score, which, together with the inclusion of other MRI-based markers like EPVS, perhaps explains the superior predictive performance of the FENS score over the ALM score. Therefore, we propose the use of the FENS score for risk stratification of ESUS patients who have a brain MRI and the ALM score for risk stratification of ESUS patients who have a brain CT.

The main strength of this study is that the prognostic score is based on quantitative MRI-based parameters which can be assessed easily, accurately, and reliably in daily clinical practice. Another strength is the excellent predictive and discriminative performance of the score. The main limitation is that it is a single-center retrospective study and a relatively small sample size. Another limitation is the lack of external validation, but we have used the bootstrap method for internal validation and compared FENS scores and ALM scores to ensure the validation of this finding. In addition, given that the follow-up was conducted from 06/2022 to 07/2022, the potential bias may be inevitable.

In conclusion, this study proposes the MRI-based FENS score, which can provide excellent predictive performance for recurrent stroke/TIA and may assist in risk stratification of ESUS patients. Confirmation of these results in other cohorts is warranted.

Author Contributions

Q.Y.L., Y.J.D., X.Q.L., and X.H.W. contributed to the acquisition of data; Q.Y.L. and Y.J.D. analyzed imaging data and drafted the manuscript; H.S.C. and G.N. contributed to the study design and critically edited the manuscript.

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Conflict of Interest

None declared.

Data Availability Statement

Data are available upon reasonable request.

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